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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/904,938	07/12/2001	Avi Ashkenazi	GNE.1618P2C35	3143
35489	7590	07/16/2004	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CO 94025-3506			SPECTOR, LORRAINE	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 07/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/904,938	Applicant(s) ASHKENAZI ET AL.	
	Examiner Lorraine Spector, Ph.D.	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 44-46 and 49-51 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 44-46, 49-51 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Claims 44-46 and 49-51 are pending and under consideration.

Formal Matters:

The new title of the invention is acknowledged.

Priority Determination:

The disclosed protein has no utility; see rejection, below. Accordingly, for the purposes of applying prior art, the effective filing date of this application is its actual filing date, 7/12/2001.

Applicants argue that priority is merited at least to the filing date of PCT/US/00/03565, filed 2/11/00. Applicants are requested to submit the appropriate pages of the PCT document so that the Examiner can verify the priority claim. Pending receipt of such, priority stands at 7/12/2001.

However, it is noted that the above issue is moot, as there are no remaining rejections over the prior art.

Objections and Rejections under 35 U.S.C. §101 and §112:

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 44-46 and 49-51 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility for reasons cited in the previous Office Action mailed 1/14/2004, at pages 3-4. Applicant argument, filed 4/16/2004 has been fully considered, but is not deemed persuasive, for reasons below:

At page 10 of the response, applicants assert that "PRO304 showed approximately 2.00-3.204 fold amplification in 7 primary lung tumors, figures which are way above figures

considered significant.” This argument has been fully considered but is not deemed persuasive because (a) applicants have not provided any declaratory evidence of the 2.00-3.204 fold amplification, most especially how the delta Ct values at page 230-234 have been extrapolated to three decimal places of amplification, (b) applicants have failed to provide fact or evidence that the figures are “way above figures considered significant”, as asserted, nor what such figures are deemed to signify. As set forth in the previous Office Action,

“Even though the data demonstrated a slight increase in copy number of PRO304 nucleic acids in primary lung squamous cell carcinoma cells (see pages 222-225 of the specification), such is not be indicative of a use of the encoded polypeptide as a diagnostic agent. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). A slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. The preliminary data were not supported by analysis of mRNA or protein expression, for example. Thus, the data do not support the implicit assertion that PRO304 can be used as a cancer diagnostic. Significant further research would have been required of the skilled artisan to determine whether PRO304 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic, and thus the implicitly asserted utility is not substantial.

The Examiner’s position that an increase in nucleic acid copy number is not predictive of a similar association for protein is supported by the prior art. The art does not recognize that protein levels are increased when gene amplification occurs. For example, Pennica et al., teach that WISP1 and WISP2 are both amplified in tumors, but RNA expression of WISP2 was *reduced* in 79% of tumors, while that of WISP1 was *increased* in 84% of tumors (see abstract). See also Konopka (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that “Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template” (see abstract). Finally, see Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level, and found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50-fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Therefore, the art indicates that it is not the norm that gene amplification, or increased transcription, results in increased protein levels. Accordingly, the showing that the DNA encoding PRO304 is present in increased copy number in a particular tumor type is not sufficient to establish any utility for the protein encoded thereby or antibody that binds to the protein.”

It remains that there was only minor amplification of the *nucleic acid* encoding the claimed protein in 8 of twenty tested lung tumor explants/biopsies, 1 of 9 adenocarcinomas, 5 of 11 squamous cell carcinomas, and 1 of 2 adeno/squamous cell carcinomas (presumably ambiguous

specimens). Such minor amplification of the nucleic acid, in a minority of the tested tumor cells, is not sufficient to convey utility to the claimed protein.

Applicants arguments pertaining to a declaration by Dr. Avi Ashkenazi, one of the inventors, will not be addressed, as no such declaration accompanied applicants response.

Applicants argument that “there is expected to be a correlation between gene amplification and protein overexpression”, with reference to an article by Celis et al., has been fully considered but is not deemed persuasive. The Celis article states that the art teaches that “there is not a good correlation between mRNA and protein levels in human liver, implying that gene-based expression data may be of limited value in the process of drug discovery” (see page 13, first column. In the same column, the portion quoted by applicants occurs. However, as it appears in the paper and at page 11 of the response, Orntoft et al. *could only compare the levels of about 40 well-resolved and focused abundant proteins.*” As the Orntoft reference appears not to have been published, the Examiner cannot evaluate how high the amplification of the nucleic acids in question was, i.e. whether it was comparable to the mere 2-3 fold amplification found for PRO304. It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors, and an associated rise in level of the encoded protein. Accordingly, it remains that the significance of the gene amplification data is questionable, and cannot be predictably extrapolated as applying to the claimed protein.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 44-46 and 49-51 also remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Deposit requirement:

Claims 44-46 and 49-51 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The deposit of biological organisms is considered by the Examiner to be necessary for enablement of the current invention (see 37 C.F.R.§1.808(a)). Examiner acknowledges the deposit of organisms under accession number ATCC 209482 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, applicants must state that the deposit will be maintained for a term of at least 30 years *and at least five (5) years after the most recent request for the furnishing of a sample of the deposit was received by the depository*. See 37 C.F.R.§1.806.

Applicants deposit statement, filed 4/16/04 is noted. However, it continues to omit the phrase italicized above.

Advisory Information:

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

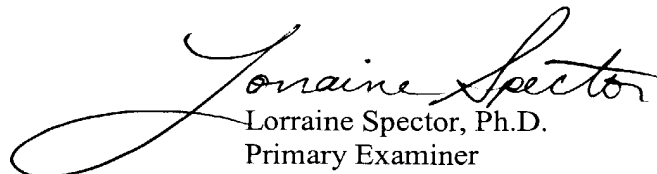
Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number is 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Lorraine Spector, Ph.D.
Primary Examiner

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7/13/2004